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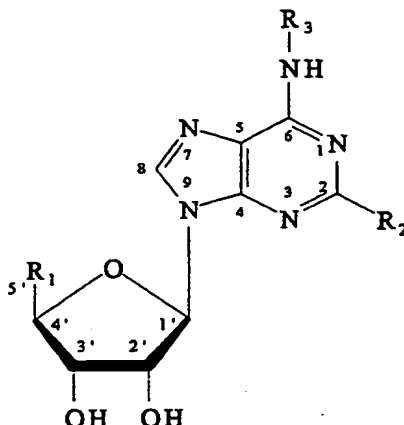
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07H 19/467, A61K 31/70		A1	(11) International Publication Number: WO 95/02604 (43) International Publication Date: 26 January 1995 (26.01.95)
(21) International Application Number: PCT/US94/07835 (22) International Filing Date: 13 July 1994 (13.07.94) (30) Priority Data: 091,109 13 July 1993 (13.07.93) US 163,324 6 December 1993 (06.12.93) US (71) Applicant: THE UNITED STATES OF AMERICA , represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health [US/US]; Office de Technology Transfer, Box OTT, Bethesda, MD 20892-9902 (US). (72) Inventors: JACOBSON, Kenneth, A. ; 116506 Fulham Street, Silver Spring, MD 20902 (US). GALLO-RODRIGUEZ, Carola ; Avenue Santa Fé 2533 8°A, RA-1425 Buenos Aires (AR). VAN GALEN, Philip, J., M. ; Titus Brandsmaplein 40, NL-5342 EP Oss (NL). VON LUBITZ, Dag, K., J., E. ; 6329 Dorset Drive, Alexandria, VA 22310 (US). JEONG, Heaok, Kim ; 5603 Alderbrook Court #104, Rockville, MD 20851 (US). (74) Agents: KILYK, John, Jr. et al. ; Leydig, Voit & Mayer, Ltd., Suite 4900, Two Prudential Plaza, Chicago, IL 60601-6780 (US).			(81) Designated States: AU, CA, JP , European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: A₃ ADENOSINE RECEPTOR AGONISTS			
(57) Abstract The present invention provides N ⁶ -benzyladenosine-5'-N-uronamide and related substituted compounds, particularly those containing substituents on the benzyl and/or uronamide groups, and modified xanthine ribosides, as well as pharmaceutical compositions containing such compounds. The present invention also provides a method of selectively activating an A ₃ adenosine receptor in a mammal, which method comprises acutely or chronically administering to a mammal in need of selective activation of its A ₃ adenosine receptor a therapeutically effective amount of a compound which binds with the A ₃ receptor so as to stimulate and A ₃ receptor-dependent response.			

WHAT IS CLAIMED IS:

1. A compound of the formula



- 5 wherein R₁ is R^aR^bNC(=O) or HOR^c, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, C₁-C₁₀ boc-aminoalkyl, and
 10 C₃-C₁₀ cycloalkyl, or are joined together to form a heterocyclic ring containing two to five carbon atoms, and R^c is selected from the group consisting of C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, C₁-C₁₀ boc-aminoalkyl, and C₃-C₁₀ cycloalkyl, R₂ is selected from
 15 the group consisting of hydrogen, halo, C₁-C₁₀ alkylethers, amino, C₁-C₁₀ alkylamino, C₂-C₁₀ alkenes, C₂-C₁₀ alkynes, thio, and C₁-C₁₀ alkylthio, and R₃ is selected from the group consisting of R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a
 20 phenylethyl or benzyl group substituted in one or more positions with a substituent selected from the group consisting of C₁-C₁₀ alkyl, amino, halo, C₁-C₁₀ haloalkyl, nitro, hydroxy, acetamido, C₁-C₁₀ alkoxy, and sulfo.

- 25 2. The compound of claim 1, wherein R₁ is R^aR^bNC(=O), wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen,

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C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, and C₃-C₁₀ cycloalkyl, R₂ is selected from the group consisting of hydrogen, halo, C₁-C₁₀ alkylethers, amino, C₂-C₁₀ alkenes, and C₂-C₁₀ alkynes, and R₃ is selected from the group consisting of R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a benzyl group substituted in one or more positions with a substituent selected from the group consisting of C₁-C₁₀ alkyl, amino, halo, C₁-C₁₀ haloalkyl, nitro, hydroxy, acetamido, C₁-C₁₀ alkoxy, and sulfo.

3. The compound of claim 2, wherein R₂ is hydrogen or halo.

4. The compound of claim 2, wherein R^a is hydrogen and R₂ is hydrogen.

5. The compound of claim 4, wherein R₃ is unsubstituted benzyl.

6. The compound of claim 5, wherein R^b is a C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl.

7. The compound of claim 6, wherein R^b is a C₁-C₁₀ alkyl.

8. The compound of claim 7, wherein R^b is methyl.

9. The compound of claim 4, wherein R₃ is R-1-phenylethyl, S-1-phenylethyl, or a substituted benzyl.

10. The compound of claim 9, wherein R^b is a C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl.

11. The compound of claim 10, wherein R^b is a C₁-C₁₀ alkyl.

12. The compound of claim 11, wherein R^b is methyl or ethyl.

13. The compound of claim 12, wherein R₃ is a substituted benzyl.

14. The compound of claim 13, wherein R₃ is a benzyl substituted in one or more positions with a substituent selected from the group consisting of halo, amino, acetamido, C₁-C₁₀ haloalkyl, and sulfo.

15. The compound of claim 14, wherein R₃ is a halo-substituted benzyl.

16. The compound of claim 15, wherein the compound is N⁶-3-iodobenzyl-5'-N-methylcarboxamidoadenosine.

17. The compound of claim 2, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen and C₁-C₁₀ alkyl.

18. The compound of claim 1, wherein R₁ is R^aR^bNC(=O), wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, and C₃-C₁₀ cycloalkyl, R₂ is selected from the group consisting of halo, C₁-C₁₀ alkylethers, amino, C₁-C₁₀ alkylamino, C₂-C₁₀ alkenes, C₂-C₁₀ alkynes, thio, and C₁-C₁₀ alkylthio, and R₃ is selected from the group consisting of R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a benzyl group substituted in one or more positions with a substituent selected from the group consisting of C₁-C₁₀ alkyl, amino, halo, C₁-C₁₀ haloalkyl, nitro, hydroxy, acetamido, C₁-C₁₀ alkoxy, and sulfo.

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19. The compound of claim 18, wherein R^a is hydrogen and R_2 is halo, C_1 - C_{10} alkylamino, or C_1 - C_{10} alkylthio.

5 20. The compound of claim 19, wherein R_3 is a substituted benzyl.

21. The compound of claim 20, wherein R^b is a C_1 - C_{10} alkyl.

10

22. The compound of claim 21, wherein said compound is selected from the group consisting of 2-chloro- N^6 -(3-iodobenzyl)-9-[5-(methylamido)- β -D-ribofuranosyl]-adenine, N^6 -(3-iodobenzyl)-2-methylamino-9-[5-(methylamido)- β -D-ribofuranosyl]-adenine, and N^6 -(3-iodobenzyl)-2-methylthio-9-[5-(methylamido)- β -D-ribofuranosyl]-adenine.

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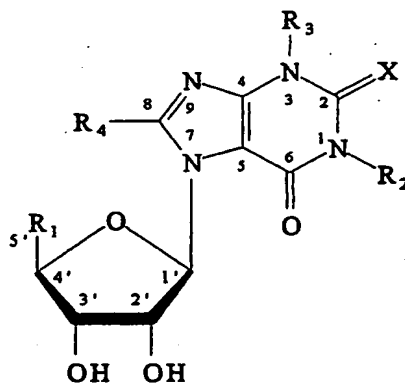
23. The compound of claim 2, wherein R_2 is a C_2 - C_{10} alkyne of the formula $R'-C\equiv C-$ where R' is a C_1 - C_8 alkyl.

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24. A compound selected from the group consisting of N^6 -benzyladenosine-5'-N-alkyluronamide- N^1 -oxide and N^6 -benzyladenosine-5'-N-dialkyluronamide- N^1 -oxide.

25

25. A compound of the formula



wherein X is O or S, R_1 is $R^aR^bNC(=O)$ or HOR^c , wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, amino, C_1 - C_{10} haloalkyl, C_1 - C_{10} aminoalkyl, and C_3 - C_{10} cycloalkyl, or
5 are joined together to form a heterocyclic ring containing two to five carbon atoms, and R^c is selected from the group consisting of C_1 - C_{10} alkyl, amino, C_1 - C_{10} haloalkyl, C_1 - C_{10} aminoalkyl, C_1 - C_{10} boc-aminoalkyl, and C_3 - C_{10} cycloalkyl, R_2 and R_3 may be the same or different
10 and are selected from the group consisting of C_1 - C_{10} alkyl, R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a phenylether or benzyl group substituted in one or more positions with a substituent selected from the group consisting of C_1 - C_{10} alkyl, amino, halo, C_1 - C_{10}
15 haloalkyl, nitro, hydroxy, acetamido, C_1 - C_{10} alkoxy, and sulfo, and R_4 is selected from the group consisting of halo, benzyl, phenyl, C_3 - C_{10} cycloalkyl, and C_1 - C_{10} alkoxy, with the proviso that if X = O, R_1 is $HOCH_2$, and R_4 = H, then R_2 and R_3 are not C_1 - C_4 alkyl.

20

26. The compound of claim 25, wherein X is O, R_1 is $R^aR^bNC(=O)$, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, amino, C_1 - C_{10} haloalkyl, C_1 - C_{10} aminoalkyl,
25 and C_3 - C_{10} cycloalkyl, R_2 and R_3 may be the same or different and are selected from the group consisting of C_1 - C_{10} alkyl, R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a benzyl group substituted in one or more positions with a substituent selected from the group
30 consisting of C_1 - C_{10} alkyl, amino, halo, C_1 - C_{10} haloalkyl, nitro, hydroxy, acetamido, C_1 - C_{10} alkoxy, and sulfo, and R_4 is selected from the group consisting of halo, benzyl, phenyl, and C_3 - C_{10} cycloalkyl.

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27. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 1.

5 28. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 2.

10 29. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 24.

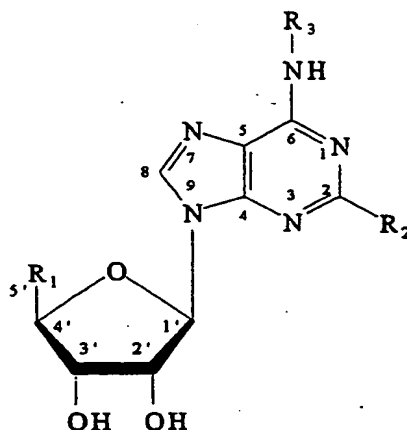
15 30. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 25.

20 31. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 26.

25 32. A method of selectively activating an A₃ adenosine receptor in a mammal, which method comprises administering to a mammal in need of selective activation of its A₃ adenosine receptor a therapeutically effective amount of a compound which binds with the A₃ receptor so as to stimulate an A₃ receptor-dependent response.

33. The method of claim 32, wherein said compound has the formula

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wherein R₁ is R^aR^bNC(=O) or HOR^c, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, C₁-C₁₀ boc-aminoalkyl, and C₃-C₁₀ cycloalkyl, or are joined together to form a heterocyclic ring containing two to five carbon atoms, and R^c is selected from the group consisting of C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, and C₃-C₁₀ cycloalkyl, R₂ is selected from the group consisting of hydrogen, halo, C₁-C₁₀ alkylethers, amino, C₁-C₁₀ alkylamino, C₂-C₁₀ alkenes, C₂-C₁₀ alkynes, thio, and C₁-C₁₀ alkylthio, and R₃ is selected from the group consisting of R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a phenylethyl or benzyl group substituted in one or more positions with a substituent selected from the group consisting of C₁-C₁₀ alkyl, amino, halo, C₁-C₁₀ haloalkyl, nitro, hydroxy, acetamido, C₁-C₁₀ alkoxy, and sulfo.

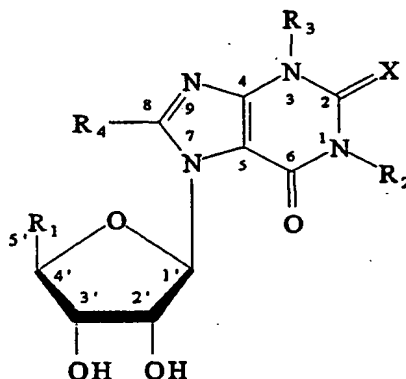
34. The method of claim 33, wherein R₁ is R^aR^bNC(=O), wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, and C₃-C₁₀ cycloalkyl, R₂ is selected from the group consisting of hydrogen, halo, C₁-C₁₀ alkylethers, amino,

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C₂-C₁₀ alkenes, and C₂-C₁₀ alkynes, and R₃ is selected from the group consisting of R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a benzyl group substituted in one or more positions with a substituent selected from the group consisting of C₁-C₁₀ alkyl, amino, halo, C₁-C₁₀ haloalkyl, nitro, hydroxy, acetamido, C₁-C₁₀ alkoxy, and sulfo.

35. The method of claim 32, wherein the compound is selected from the group consisting of N⁶-benzyladenosine-5'-N-alkyluronamide-N¹-oxide and N⁶-benzyladenosine-5'-N-dialkyluronamide-N¹-oxide.

36. The method of claim 32, wherein said compound has the formula



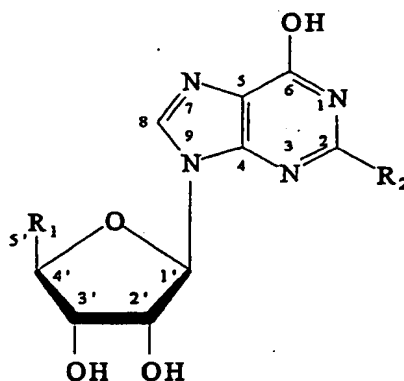
wherein X is O or S, R₁ is R^aR^bNC(=O) or HOR^c, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, C₁-C₁₀ boc-aminoalkyl, and C₃-C₁₀ cycloalkyl, or are joined together to form a heterocyclic ring containing two to five carbon atoms, and R^c is selected from the group consisting of C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, and C₃-C₁₀ cycloalkyl, R₂ and R₃ may be the same or different and are selected from the group consisting of C₁-C₁₀ alkyl, R- and S- 1-phenylethyl, an unsubstituted benzyl group, and

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a phenylether or benzyl group substituted in one or more positions with a substituent selected from the group consisting of C₁-C₁₀ alkyl, amino, halo, C₁-C₁₀ haloalkyl, nitro, hydroxy, acetamido, C₁-C₁₀ alkoxy, and sulfo, and
 5 R₄ is selected from the group consisting of halo, benzyl, phenyl, C₃-C₁₀ cycloalkyl, and C₁-C₁₀ alkoxy.

37. The method of claim 36, wherein X is O, R₁ is R^aR^bNC(=O), wherein R^a and R^b may be the same or different
 10 and are selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, and C₃-C₁₀ cycloalkyl, R₂ and R₃ may be the same or different and are selected from the group consisting of C₁-C₁₀ alkyl, R- and S- 1-phenylethyl, an unsubstituted
 15 benzyl group, and a benzyl group substituted in one or more positions with a substituent selected from the group consisting of C₁-C₁₀ alkyl, amino, halo, C₁-C₁₀ haloalkyl, nitro, hydroxy, acetamido, C₁-C₁₀ alkoxy, and sulfo, and
 20 R₄ is selected from the group consisting of halo, benzyl, phenyl, and C₃-C₁₀ cycloalkyl.

38. The method of claim 32, wherein said compound has the formula



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wherein R₁ is R^aR^bNC(=O) or HOR^c, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, amino, C₁-C₁₀

haloalkyl, C₁-C₁₀ aminoalkyl, C₁-C₁₀ boc-aminoalkyl, and C₃-C₁₀ cycloalkyl, or are joined together to form a heterocyclic ring containing two to five carbon atoms, and R^c is selected from the group consisting of C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, and C₃-C₁₀ cycloalkyl, and R₂ is selected from the group consisting of hydrogen, halo, C₁-C₁₀ alkylethers, amino, C₁-C₁₀ alkylamino, C₂-C₁₀ alkenes, C₂-C₁₀ alkynes, thio, and C₁-C₁₀ alkylthio.

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39. The method of claim 38, wherein R₁ is R^aR^bNC(=O), wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, C₁-C₁₀ boc-aminoalkyl, and C₃-C₁₀ cycloalkyl, and R₂ is selected from the group consisting of hydrogen, halo, C₁-C₁₀ alkylethers, amino, C₂-C₁₀ alkenes, and C₂-C₁₀ alkynes.

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40. The method of claim 39, wherein R^a is hydrogen and R₂ is hydrogen.

20

41. The method of claim 40, wherein R^b is a C₁-C₁₀ alkyl.

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42. The method of claim 41, wherein R^b is methyl or ethyl.

43. The method of claim 40, wherein R^b is a C₃-C₁₀ cycloalkyl.

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44. The method of claim 43, wherein R^b is cyclopropyl.

45. The method of claim 40, wherein R^b is a C₁-C₁₀ aminoalkyl.

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46. The method of claim 40, wherein R^b is a C₁-C₁₀ aminoethyl.

47. The method of claim 40, wherein R^b is a C₁-C₁₀ boc-aminoalkyl.

48. The method of claim 47, wherein R^b is boc-aminoethyl.

49. The method of claim 40, wherein the compound is selected from the group consisting of 5'-N-aminoethylamino-carboxamidoadenosine and 5'-N-boc-aminoethylamino-carboxamidoadenosine.

50. The method of claim 40, wherein R^b is hydrogen.

51. The method of claim 32, wherein said compound is a 1,3-R₁R₂-xanthine-7-riboside, wherein R₁ and R₂ may be the same or different and are selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, benzyl, and C₃-C₁₀ cycloalkyl, or are joined together to form a heterocyclic ring containing two to five carbon atoms.

52. The method of claim 51, wherein said compound is a 1,3-R₁R₂-xanthine-7-riboside, wherein R₁ and R₂ may be the same or different and are selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, benzyl, and C₃-C₁₀ cycloalkyl.

53. The method of claim 52, wherein said compound is a 1,3-dialkylxanthine-7-riboside.

54. The method of claim 52, wherein said compound is 1,3-dibutylxanthine-7-riboside.

55. The method of claim 32, wherein said compound is a 5'-R₃-1,3-R₁R₂-xanthine-7-riboside, wherein R₁ and R₂ are selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, benzyl, and C₃-C₁₀ cycloalkyl, or are joined together to form a heterocyclic ring containing two to five carbon atoms, and R₃ is selected from the group consisting of C₁-C₁₀ alkoxy carbonyl and aminocarbonyl, wherein the amino group is unsubstituted or substituted at one or more positions with a C₁-C₁₀ alkyl.

56. The method of claim 55, wherein said compound is a 5'-R₃-1,3-R₁R₂-xanthine-7-riboside, wherein R₁ and R₂ are selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, amino, C₁-C₁₀ haloalkyl, C₁-C₁₀ aminoalkyl, benzyl, and C₃-C₁₀ cycloalkyl, and R₃ is selected from the group consisting of C₁-C₁₀ alkoxy carbonyl and aminocarbonyl, wherein the amino group is unsubstituted or substituted at one or more positions with a C₁-C₁₀ alkyl.

57. The method of claim 56, wherein said compound is a 5'-R₃-1,3-dibutylxanthine-7-riboside, wherein R₃ is selected from the group consisting of C₁-C₁₀ alkoxy carbonyl and aminocarbonyl, wherein the amino group is unsubstituted or substituted at one or more positions with a C₁-C₁₀ alkyl.

58. The method of claim 57, wherein said compound is 5'-methyaminocarbonyl-1,3-dibutylxanthine-7-riboside.

59. The method of claim 51, wherein said compound is chronically administered.

60. The method of claim 55, wherein said compound is chronically administered.

61. The method of claim 58, wherein said compound is chronically administered.

5 62. The method of claim 32, wherein said mammal has or is at risk of having a condition, disorder, or disease state associated with the cellular release of inositol-1,4,5-triphosphate or diacylglycerol.

10 63. The method of claim 32, wherein said mammal has or is at risk for hyperactivity and said compound in binding to said A_3 adenosine receptors functions as a locomotor depressant.

15 64. The method of claim 32, wherein said mammal has or is at risk for hypertension and said compound in binding to said A_3 adenosine receptors functions as a hypotensive agent.

20 65. The method of claim 32, wherein said mammal has or is at risk for anxiety and said compound in binding to said A_3 adenosine receptors functions as an anxiolytic agent.

25 66. The method of claim 32, wherein said mammal has or is at risk for cerebral ischemia and said compound in binding to said A_3 adenosine receptors functions as a cerebroprotectant.

30 67. The method of claim 32, wherein said mammal has or is at risk for seizures and said compound in binding to said A_3 adenosine receptors functions as an antiseizure agent.

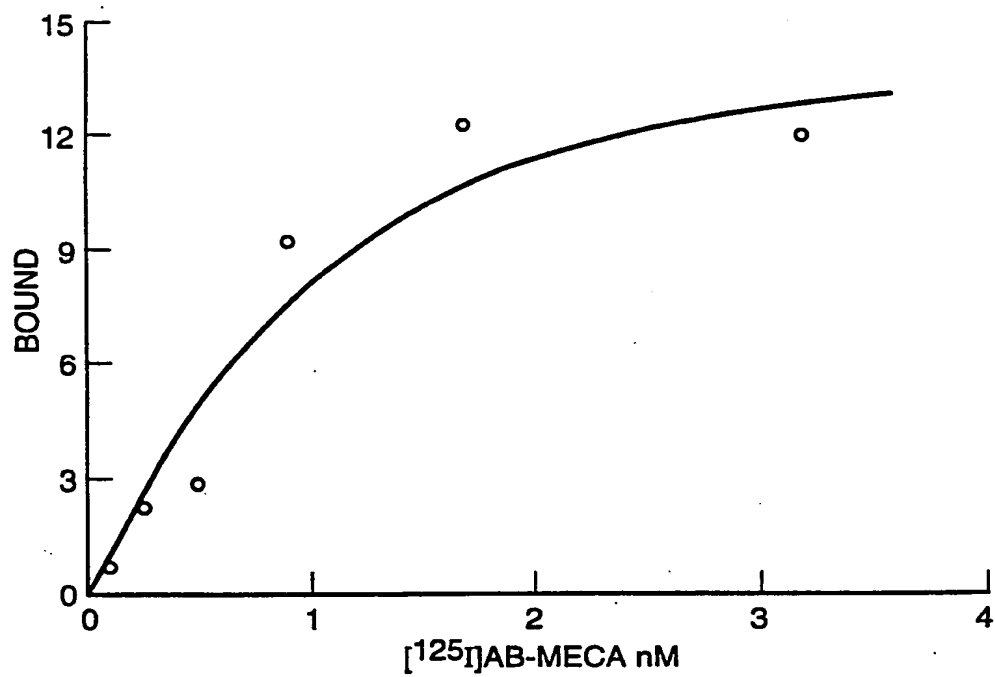
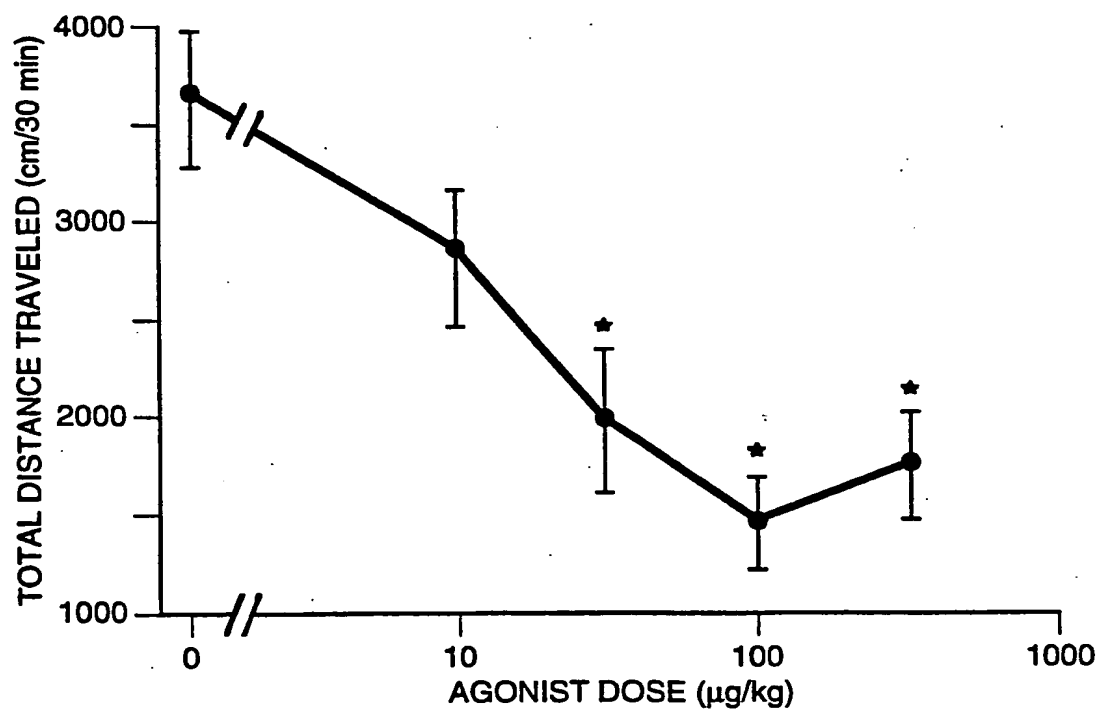
35 68. An assay which comprises providing a compound of claim 1 which has been labeled, contacting a sample with said labeled compound under conditions sufficient to

effect binding between said labeled compound and a component of said sample, and determining whether said binding occurred.

5 69. An assay which comprises providing a compound
of claim 24 which has been labeled, contacting a sample
with said labeled compound under conditions sufficient to
effect binding between said labeled compound and a
component of said sample, and determining whether said
10 binding occurred.

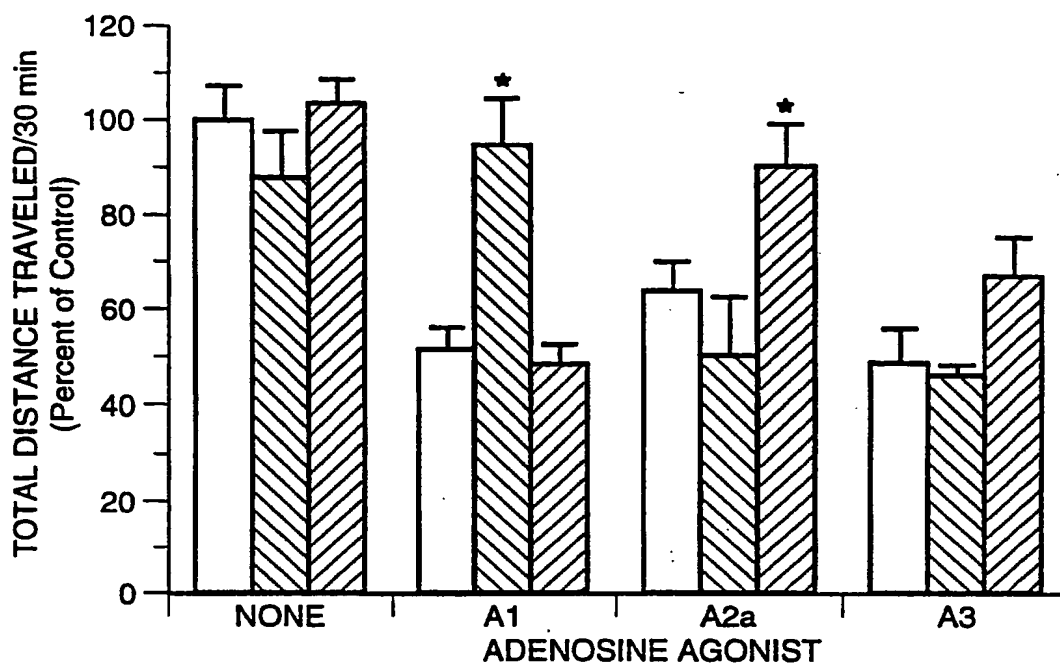
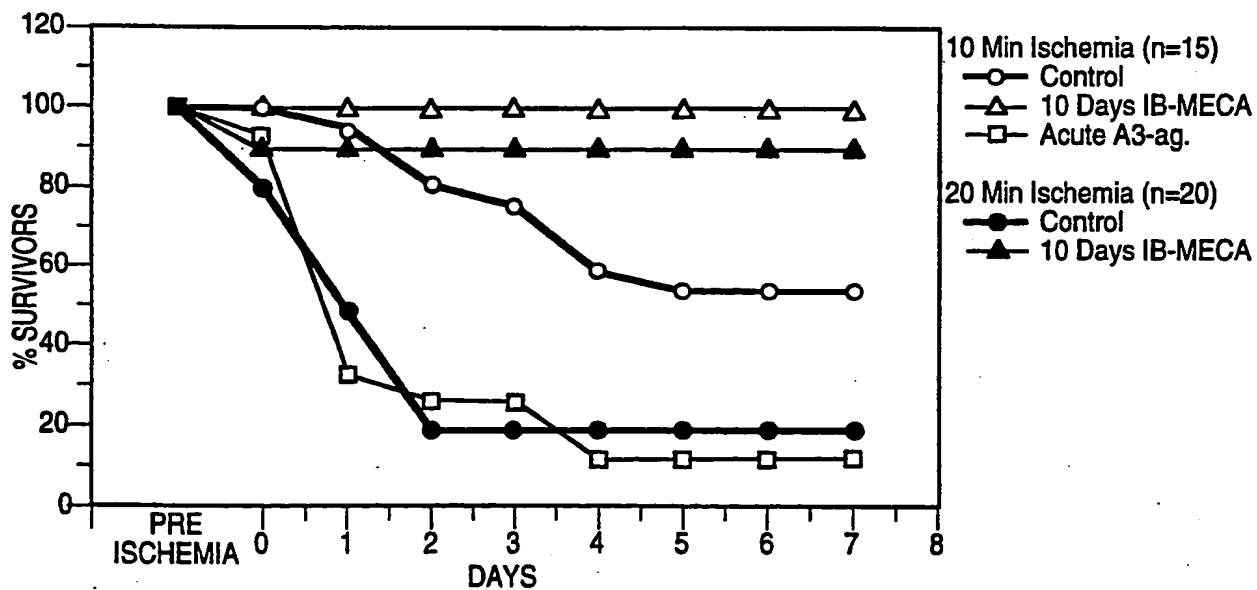
 70. An assay which comprises providing a compound
of claim 25 which has been labeled, contacting a sample
with said labeled compound under conditions sufficient to
15 effect binding between said labeled compound and a
component of said sample, and determining whether said
binding occurred.

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**FIG. 1****FIG. 2**

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**FIG. 3****FIG. 4**

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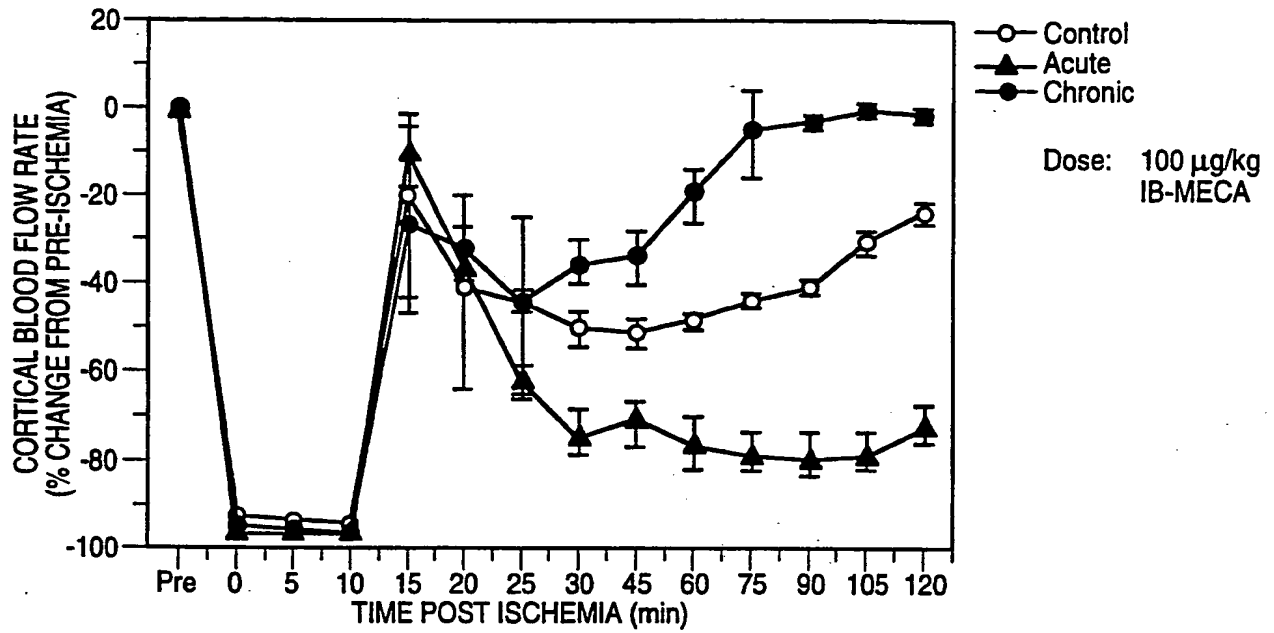


FIG. 5

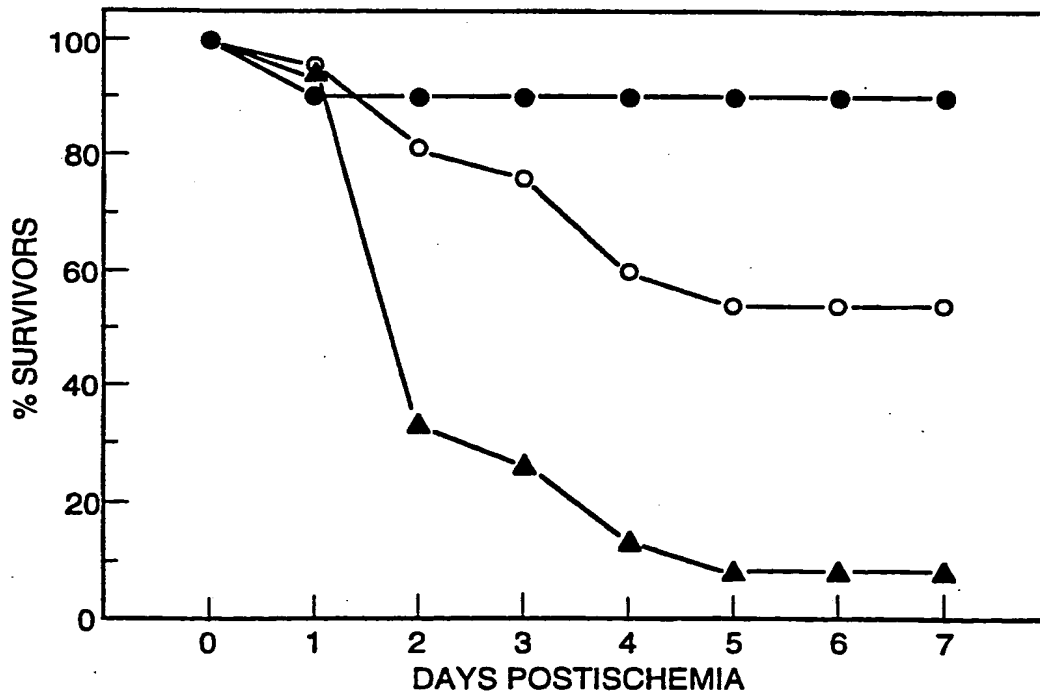
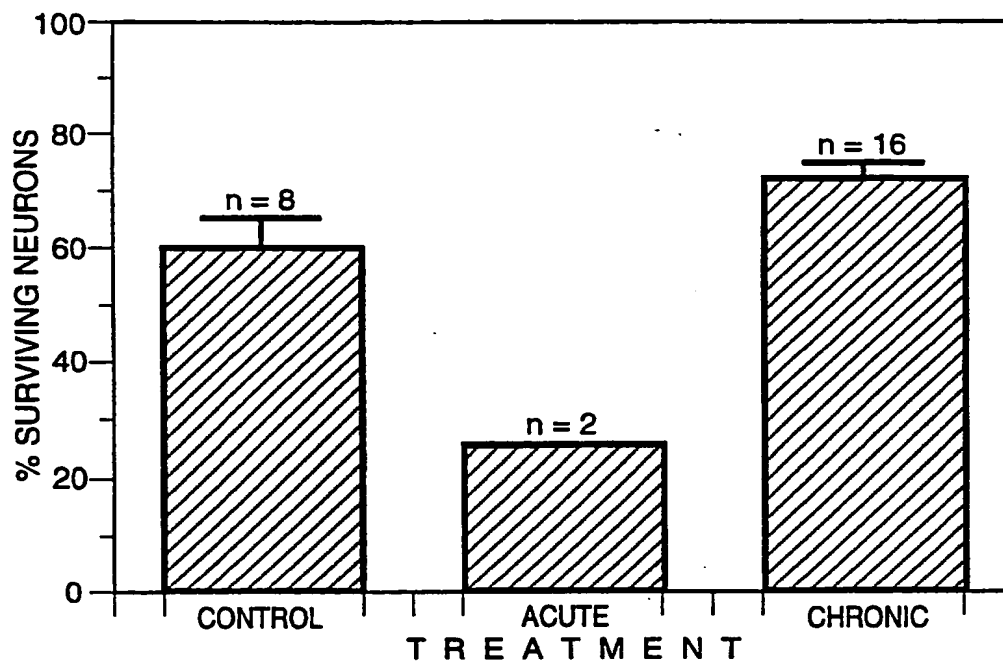
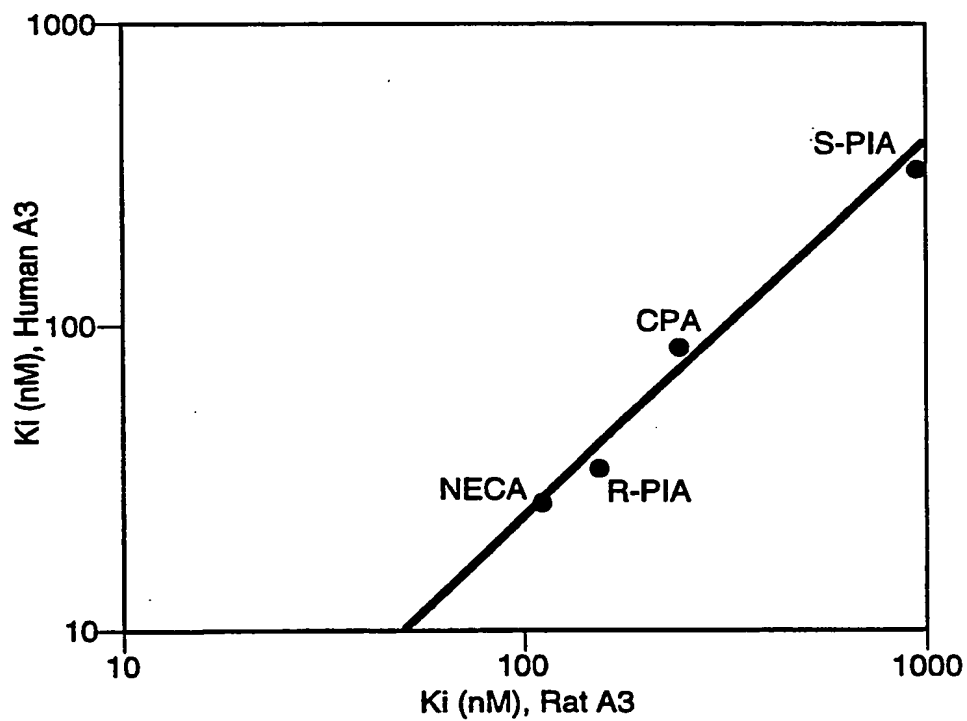


FIG. 6

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**FIG. 7****FIG. 8**

INTERNATIONAL SEARCH REPORT

Intel. Appl. No.

PCT/US 94/07835

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H19/167 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,86 00310 (NELSON RESEARCH AND DEVELOPMENT COMPANY) 16 January 1986 See the Whole Document, but especially, compounds 23 and 25 on page 11, compound 21 on page 12, compounds 35,36 and 38 on page 15 -----	1-4, 9-15,17
X	DE,A,25 24 284 (BOEHRINGER MANNHEIM GMBH) 28 October 1976 see page 4; examples 1,1a,and,1b ----- -/--	1

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *"A" document defining the general state of the art which is not considered to be of particular relevance
- *"E" earlier document but published on or after the international filing date
- *"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *"O" document referring to an oral disclosure, use, exhibition or other means
- *"P" document published prior to the international filing date but later than the priority date claimed

- *"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *"&" document member of the same patent family

Date of the actual completion of the international search

31 October 1994

Date of mailing of the international search report

16. 11. 94

Name and mailing address of the ISA

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Fax (+ 31-70) 340-3016

Authorized officer

Scott, J

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF MEDICINAL CHEMISTRY, vol.35, no.3, 7 February 1992, WASHINGTON US pages 407 - 422 K.A.JACOBSON ET AL. 'Adenosine Receptors: Pharmacology, Structure-Activity Relationships, and Therapeutic Potential.' see examples 12-14	1
A	see the whole document ---	1-70
X	JOURNAL OF MEDICINAL CHEMISTRY, vol.29, no.6, June 1986, WASHINGTON US pages 989 - 996 S.KUSACHI ET AL. 'Dog Coronary Artery Adenosine Receptor: Structure of teh N6-Aryl Subregion.' See Table 1, compounds 14-31 and 47-63 ---	1
X	CHEMICAL ABSTRACTS, vol. 72, no. 5, 2 February 1970, Columbus, Ohio, US; abstract no. 21921c, K.KOCH ET AL. '2-Aminoadenosine Derivatives with Cardiac Activity.' page 352 ;column 1 ; see abstract & SA,A,6 805 477 (BOEHRINGER, C.F., UND SOEHNE GMBH) 28 January 1969 ---	1
X	CHEMICAL ABSTRACTS, vol. 70, no. 19, 12 May 1969, Columbus, Ohio, US; abstract no. 88212z, W.KAMPE ET AL. 'Adenosines' page 394 ;column 1 ; see abstract & SA,A,6 707 630 (BOEHRINGER C.F., UND SOEHNE GMBH) 21 December 1966 ---	1
X	NUCLEOSIDES AND NUCLEOTIDES, vol.12, no.5, 1993 pages 431 - 439 MOSSHILI A.N. MOSSELHI 'Ribosylation of 8-Substituted Theophylline Derivatives.' See page 432, scheme 1, compound 7 ---	25
P,X	JOURNAL OF MEDICINAL CHEMISTRY, vol.37, no.5, 4 March 1994, WASHINGTON US pages 636 - 646 C.GALLO-RODRIGUEZ ET AL. 'Structure-Activity Relationships of N-6-Benzyladenosine-5'-Uronamides as A3 Selective Adenosine Agonists.' see the whole document --- -/--	1-17

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BRITISH JOURNAL OF PHARMACOLOGY, vol.109, no.1, May 1993 pages 3 - 5 J.R.FOZARD ET AL. 'Adenosine A3 Receptors Mediate Hypotension in the Angiotensin II-supported Circulation of the Pithed Rat.' cited in the application see the whole document ---	1
A	NUCLEOSIDES AND NUCLEOTIDES, vol.10, no.5, 1991 pages 1191 - 1193 P.J.M.VAN GELEN ET AL. 'Xanthine-7-Ribosides as Adenosine Receptor Antagonists: Further Evidence For Adenosine's Anti Mode of Binding.' cited in the application see the whole document -----	25

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/07835

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 32-67
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 32-67 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 94/07835

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8600310	16-01-86	US-A- 5310731 AU-B- 590724 AU-A- 4497285 EP-A, B 0191025 JP-A- 61286398	10-05-94 16-11-89 24-01-86 20-08-86 16-12-86
DE-A-2524284	28-10-76	NONE	
SA-A-6805477		NONE	
SA-A-6707630		NONE	